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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,772	OCHIAI ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/29/06; 8/28/07; 5/24/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

On 12/11/08, Applicant's Agent Traci Thompson notified the examiner that the Office Action of 11/21/08 did not include a copy of the reference Takeno et al (Appl. Microbiol. Biotechnol. 65: 419-425, 2004), and the reference was not otherwise of record. Accordingly the action of 11/21/08 is hereby withdrawn and replaced with the following action including a copy of the Takeno reference. This Action is identical to that mailed 11/21/08, except that the Takeno reference is not referred to as "of record".

An amendment was received and entered on 10/14/08. Applicant's election with traverse of group 1 is acknowledged. Traversal is on the grounds that (1) and (4) no finding of a lack of unity was made during review of the international application by the International Searching Authority, (2) when unity is found in a PCT application , there is an increased burden in evincing why a restriction requirement is necessary, (3) the Office has provided no justification relating to burden of search, and (4) the remaining subject matter of each claim after restriction does not differ from the others. Applicant's traversal is unpersuasive for the following reasons.

Regarding (1) and (4), the USPTO is not bound by the findings of the International Searching Authority, and is free to find a lack of unity if one exists regardless of the findings of the ISA. Applicant argues that MPEP 1850(II) paragraphs 4 and 5 indicate that the decision with respect to unity of invention rests with the ISA or IPEA and not the examiner of the corresponding National Stage Application. This is unpersuasive because these passages make no reference whatsoever to restriction of applications filed under 35 USC 371 that claim priority to a PCT. There is no basis

whatsoever for finding that the USPTO, in restricting claims filed under 371, is bound by conclusions regarding unity of invention set forth by the ISA in the parent PCT application.

Regarding (2) and (3), search burden is not a consideration for restriction for applications under 35 USC 371. For 371 applications, the standard for restriction is unity of invention. In this case there is no unity of invention because the technical feature linking the inventions makes no contribution over the prior art, see PCT Rules 13.1 and 13.2 and MPEP 1850 (I&II). Applicant argues that when unity is found in the PCT application, there is an increased burden in evincing why restriction is necessary, relying for support on a presentation made in a 2004 Customer Partnership Meeting by Anthony Caputa. The materials relied on by Applicant were not supplied to the Examiner, and at the time of this action were unavailable to him, so Applicant's assertion is considered to be unsupported by evidence, and is merely a presentation of opinion. Applicant cites Mr. Caputa in a passage that indicates that if the inventions now being restricted were searched and examined together in either a current application or a parent, it will be difficult to justify the assertion of burden. While the Examiner does not have the document on which Applicant relies, this passage nonetheless appears to be directed to applications filed under 35 USC 111, and does not appear to be directed to Applications filed under 35 USC 371 and claiming priority to a PCT searched by an ISA. This is because it is concerned with establishing search burden. As noted above, search burden is not a criterion in establishing unity of invention under the PCT Rules. Instead the defining criterion for establishing unity of

invention is whether or not the various claims have in common at least one technical feature that provides a contribution over the prior art, i.e. a special technical feature. In this case, there is no such special technical feature for the reasons set forth in the restriction.

Further regarding (4), the remaining subject matter clearly differs as is apparent in the groups set forth in the restriction requirement. Fatty acid elongase and desaturase genes (groups 1 and 2, respectively) are different genes encoding enzymes with different catalytic activities, and would require entirely different expression inhibition reagents. Further, 37 CFR 1.475(b) does not allow for grouping of different statutory classes of invention (i.e. products, methods of use, and/or methods of making) where there is a lack of unity of invention.

For these reasons the restriction requirement is deemed proper. Nonetheless, group 2 is rejoined as requested by Applicant. The restriction requirement is hereby made FINAL.

Claim 12-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/14/08.

Claims 1-11 are under consideration.

Priority

The effective filing date of the instant claims is no earlier than the filing date of PCT/JP2005/05786, i.e. 3/26/05 because, although Applicant claims priority to JAPAN 2004-107512, filed 3/31/2004, and a copy of this foreign priority document is in the file, no translation of this Japanese language document has been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Drawings

No drawings were submitted with the application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Certik et al (Trends in Biotechnology 16(12): 500-505, 1998, of record), Ueda (J. Neurogenetics 15(3-4): 193-204, 2001, of record), and Mackenzie et al (App. Env. Microbiol. 66(1): 4655-4661, 2000, of record).

Certik taught that there was an increasing demand for biologically active polyunsaturated fatty acids (PUFAs) and that oleaginous filamentous fungi possess several advantages as a source for PUFAs. In particular, *Mortierella alpina* is disclosed

as one of the best producers of various types of PUFA, and is a strain which has several advantages including: it is a highly oleaginous strain; its lipogenesis is simply regulated; it is one of the most well-studied microorganisms producing PUFAs; the strain is able to incorporate and transform exogenous fatty acids; it is amenable to molecular-genetic study; and the strain can be used in an industrial scale. Certik also disclosed the use of such fungi for producing lipids, wherein fatty acid desaturase activity was decreased by mutation or by use of specific enzyme inhibitors. See abstract, paragraph bridging left and right columns on page 500; paragraph bridging pages 500 and 501; page 501, left column, first full paragraph; and Fig. 1 on page 501. More specifically, Certik noted that mutants with defective desaturases such as Δ^5, Δ^6, Δ^9, Δ^{12}, and ω^3 are worthwhile as producers of useful PUFAs, and for providing valuable information on PUFA biosynthesis in *M. alpina*. Page 501, left column, last paragraph.

Ueda taught that RNAi provided a means of selectively inhibiting expression of genes of choice that was conserved across a wide variety of organisms including plants animals and fungi. Methods include stably transfecting target organisms with heritable expression constructs encoding RNAi agents. See abstract; page 195, second full paragraph; Fig. 1B on page 196; last paragraph on page 197; and second full paragraph on page 199.

Mackenzie et al (App. Env. Microbiol. 66(1): 4655-4661, 2000) taught means for delivering genetic material to *Mortierella* for stable expression of genes of interest. See abstract, and "Vector construction and transformation of *M. alpina"* at page 4656.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use RNAi to inhibit the activity of any of the Δ^5, Δ^6, Δ^9, Δ^{12}, or ω^3 desaturases of *M. alpina*. One would have been motivated to inhibit these enzymes because Certik indicated that strains defective in these enzymes were useful as producers of PUFAs as well as for providing valuable information on PUFA biosynthesis. It would have been obvious to use siRNA to suppress expression of the genes because use of this method allows one to specifically and selectively target any desaturase gene of interest for which target sequence information was available, obviating the need to screen for randomly occurring mutants. Further, one would have had a reasonable expectation of success in view of the fact that RNA interference was known to function in fungi (see Ueda) , and in view of the availability of vectors and techniques for establishing stable expression of heterologous genes in *M. alpina* (see Mackenzie).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Takeno et al (Appl. Microbiol. Biotechnol. 65: 419-425, 2004).

Takeno disclosed the establishment of a microprojectile bombardment-based transfection system of M. alpina, and the establishment of stable transfectants. See abstract. The authors also stated that they "have aimed to overexpress or destroy a gene involved in PUFA biosynthesis". Accordingly it would have been obvious to one of ordinary skill in the art at the time of the invention to have used the method of Takeno to suppress the expression of a PUFA biosynthetic gene by destroying the gene, as

suggested by Takeno. Note that Takeno is available as prior art because, although Applicant claims priority to a Foreign Priority Document in the Japanese language that antedates Takeno, no translation of that document has been made of record, therefore the effective filing date of the instant claims is no earlier than 3/26/05, as discussed above.

Claims 2-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takeno et al (Appl. Microbiol. Biotechnol. 65: 419-425, 2004) as applied to claim 1 above, and further in view of Ueda (J. Neurogenetics 15(3-4): 193-204, 2001, of record) and Mackenzie et al (App. Env. Microbiol. 66(1): 4655-4661, 2000, of record).

Takeno disclosed the establishment of a microprojectile bombardment-based transfection system of M. alpina, and the establishment of stable transfectants. See abstract. The authors also stated that they "have aimed to overexpress or destroy a gene involved in PUFA biosynthesis". Accordingly it would have been obvious to one of ordinary skill in the art at the time of the invention to have used the method of Takeno to suppress the expression of a PUFA biosynthetic gene by destroying the gene, as suggested by Takeno.

Takeno did not disclose the use of RNAi to destroy the PUFA biosynthetic gene.

Ueda taught that RNAi provided a means of selectively inhibiting expression of genes of choice that was conserved across a wide variety of organisms including plants animals and fungi. Methods include transfecting target organisms with heritable expression constructs encoding RNAi agents. See abstract; page 195, second full

paragraph; Fig. 1B on page 196; last paragraph on page 197; and second full paragraph on page 199.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use siRNA to inhibit expression of a PUFA biosynthesis gene. One of ordinary skill appreciates that genetic methods for physically destroying a gene require recombination events at a precise site, i.e. the site of the gene of interest. However, Mackenzie taught that it was difficult to obtain stable, chromosomally-integrated transformants in *M. alpina*, and that to do so it was necessary to take advantage of the large number of repetitive rDNA sites in the *M. alpina* genome by targeting them for homologous recombination. See page 4655, right column , second sentence of first full paragraph. *M. alpina* contains 150-200 tandemly repeated copies of the rDNA locus per haploid genome. Use of vectors designed to integrate at rDNA loci increases the probability of obtaining stable integrants. See page 4658, left column, first full paragraph, and right column, lines 3-9. Thus one of ordinary skill would conclude that there would be a greater expectation of success in suppressing expression of a target gene if one used siRNA expression vectors targeted to integrate in *M. alpina* rDNA, than if one sought to knock out a specific *M. alpina* gene by homologous recombination. Thus the invention as a whole was prima facie obvious.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Certik et al (Trends in Biotechnology 16(12): 500-505, 1998, of record), Ueda (J. Neurogenetics 15(3-4): 193-204, 2001, of record), and Mackenzie et al (App. Env. Microbiol. 66(1):

4655-4661, 2000, of record) as applied to claims 1-4, 6-9, and 11 above, and further in view of White et al (US 6,939,704).

The teachings of Certik, Ueda, and Mackenzie are discussed above and can be combined to render obvious methods of suppressing the expression of a PUFA biosynthetic gene in *M. alpina* using RNAi methodology.

These references did not teach gene delivery by electroporation or particle bombardment.

White taught that filamentous fungi could be transfected by several methods including calcium chloride treatment of protoplasts, electroporation, and particle bombardment. See column 12, lines 22-31

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any of calcium chloride treatment of protoplasts, electroporation, or particle bombardment to deliver nucleic acids to M. alpina, because these techniques were suggested for use with filamentous fungi.

Thus the invention as a whole was prima facie obvious.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Certik et al (Trends in Biotechnology 16(12): 500-505, 1998, of record), Ueda (J. Neurogenetics 15(3-4): 193-204, 2001, of record), and Mackenzie et al (App. Env. Microbiol. 66(1): 4655-4661, 2000, of record) as applied to claims 1-4, 6-9, and 11 above, and further in view of Parker-Barnes et al (Proc. Nat. Acad. Sci. USA 97(15): 8284-8289, 2000, of record).

The teachings of Certik, Ueda, and Mackenzie are discussed above and can be combined to render obvious methods of suppressing the expression of a PUFA biosynthetic gene in *M. alpina* using RNAi methodology. Certik also disclosed that fatty acid elongase was required in PUFA biosynthesis.

Parker-Barnes discovered a gene encoding a fatty acid elongase gene from *M. Alpina*.

It would have been obvious to one of ordinary skill in the art at the time of the invention to suppress expression of the M. alpina elongase gene of Parker-Barnes using RNAi methodology. One would have been motivated to do so in order to evaluate the function of the gene and its interactions with other genes in the fatty acid biosynthesis pathway. See e.g. Ueda, abstract.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official

central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635